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Data Standards Will Be Required: Challenges for Medical Device Submissions

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ABSTRACT

On October 25, 2012, the FDA made a clear statement at the annual CDISC Interchange in Baltimore, Maryland that electronic standards such as those developed by CDISC will be required. This has particular implications for medical device submissions due to the lack of familiarity with CDISC standards by sponsors and the FDA. While the FDA does accept SDTM domains for medical device submissions, there is currently no consistent data standards and/or requirements for medical device submissions. CDRH is required to develop standards for submissions and the work of the Device Team will be important in developing these standards. The Device Team (in cooperation with the FDA) has developed seven new SDTM domains. However, much work remains to define the standards for submission of medical device data in an electronic format. To that end a CDISC pilot with CDRH is planned. This paper will focus on the challenges for sponsors and the FDA in defining these standards.

INTRODUCTION

Medical devices are usually submitted to the FDA's Center for Devices and Radiological Health (CDRH), while all HIV and blood-screening-donation devices are submitted to the Center for Biologics Evaluation and Research (CBER). This paper will primarily focus on medical device submissions to CDRH. Electronic files (.pdf files and/or SAS® transport files) may be submitted, but paper is the primary medium for submissions to CDRH. CDRH does receive domains that are modeled after SDTM. However, there are no consistent standards or requirements for SDTM-conformant submissions to CDRH. The CDRH webpage for data standards does list various CDISC standards such as CDASH, SDTM and ADaM (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/DataStandardsMedicalDevices/default.htm). However, much work remains to define data standards for medical device submissions.

The CDISC SDTM Device Team (Device Team) was started in May, 2006 with the goal of developing standard domains to help sponsors submit data using CDISC standards to CDRH. In February, 2009 the team expanded with the help of AdvaMed and the CDASH team (Smoak 2007, Smoak 2008, Smoak 2010). The Device Team compared medical device CRFs with CDASH (data capture) standards to identify the types of data routinely collected but not currently represented in CDISC domains (Shiralkar 2010). The Device Team then developed seven new SDTM-based domains towards the goal of being able to submit CDISC-conformant data to CDRH (Smoak et al 2012). The seven new SDTM-based domains are the following:

- Device Identifiers (DI)
  This is a special purpose domain which identifies a specific device unit within a submission (e.g., a 510k or PMA).

- Device In-Use (DU)
  This is a Findings domain containing the intentional values of measurements and settings of a specific device unit when the device is in use, but which may vary from subject to subject or target to target (e.g., setting on an MRI machine).

- Device Exposure (DX)
  This is an Interventions domain which records the details of a subject's exposure to a particular device under study.

- Device Events (DE)

An Events domain containing information about various kinds of device-related events, such as device malfunctions or routine calibrations. A device event may or may not be related to a subject event.

- Device Tracking and Disposition (DT)
  An Events domain that represents a record of tracking events for a particular device, such as shipping, deployment, return and destruction of a device.

- Device-Subject Relationships (DR)
  A special purpose domain linking each subject to device(s) to which they have been exposed.

- Device Properties (DO)
  A Findings domain used to submit characteristics of a particular device under study. These characteristics do not change during the course of the study and are not identifiers of the device.

Further information on these domains (in the SDTMIG for Medical Devices 1.0) is available on the CDISC website (www.cdisc.org/sdtm).

On October 25, 2012, the FDA made a clear statement at the annual CDISC Interchange that electronic standards such as those developed by CDISC, will be required for drugs, biologics, and devices. A final guidance from the FDA on data standards for submissions should be ready in 2014 (if not sooner). Sponsors will then have 24 months to comply with the guidance. This will be the first time that the FDA has had the authority to enforce guidance requiring data standards. The authority for the FDA is based on the FDA Safety and Innovation Act (FDASIA) of 2012, which President Obama signed on July 9, 2012. The FDA could refuse to accept a submission if not in the standard format.

Furthermore, the Medical Device User Fee Amendment of 2012 (http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=mdufa%20III%20performance%20goals&utm_content=1) requires CDRH and CBER to develop guidance which supports change to submission criteria. Work by the Device Team will be important in developing this guidance.

Moreover, the FDA guidance on Study Data Standards (which will be updated by the FDA due to FDASIA) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf) states that submission of electronic data applies to all types of submissions, amendments, and supplements:

- INDs, NDAs, ANDAs, IDEs, BLAs, 510(k)s, and PMAs

Thus all branches of the FDA (CDER, CBER, and CDRH) are covered by the guidance on Study Data Standards.

CHALLENGES

Currently, sponsors are not required to submit medical device data to CDRH using CDISC standards, nor are sponsors required to provide electronic submissions in the electronic Common Technical Document (eCTD) format. More medical device companies are getting trained in CDISC standards, but most medical device companies are small (less than 50 employees) and many may not even be aware of CDISC standards.

While CDRH does receive SDTM-based data, there is no requirement for CDRH to receive it. Sponsors may submit data to CDRH in a variety of formats. Thus CDRH is not used to receiving data which conforms to CDISC standards. CDRH is getting up to speed with CDISC standards, but more work is needed for them to be able to receive and review standardized electronic submissions.

Education, training and initial experience will help familiarize both sponsors and CDRH with CDISC standards. A sponsor's upper management needs to buy-in to CDISC standards and have their staff trained. CDISC's

presentation, available on their website, has useful information for presenting a business case for its standards (www.cdisc.org/membership). This business case dates from 2006, but is still useful in presenting a business case for implementing CDISC. Once people are educated in CDISC standards and there is buy-in from upper management, the process of implementing the CDISC standards can begin. Implementation could include designing eCRFs around CDASH standards, and SAS datasets designed around SDTM and ADaM standards. The sponsor's Regulatory department would also need to have meetings with CDRH about what to put in the submission.

Sponsor will have to invest a lot of time and effort to get up to speed with CDISC and implement the standards. There will be a steep learning curve. The Gartner report shows (www.cdisc.org/membership) CDSIC yields a significant return on investment. The stage at which CDISC standards are implemented within a company affects this return on investment:

- Reduce time/cost of study start-up by 70-90%
- Reduce time/cost of study conduct by 40%
- Reduce time/cost of analysis and reporting by 50%
- Reduce overall time/cost by 60%

NEXT STEPS

Much work remains to realize the goal of all medical device data being submitted to CDRH in CDISC-conforming standards and in an eCTD. The Device Team has made progress in developing seven new SDTM domains. The Device Team's future work includes:

- Controlled terminology
  - This sub-team will develop controlled terminology for the new device domains.
- CDASH/CRF
  - This sub-team will develop the CDASH/CRF elements for the new device domains.
- ADaM
  - This sub-team will liaise with the ADaM (analysis) team to determine what links do or can exist between device domains and ADaM.
- Diagnostics and other areas that require specific standards
  - Specific types of medical devices may require additional standards. A diagnostics sub-team has been formed to develop standards for diagnostics.
- Granularity and components
  - The initial device domains assumed tracking and management of a single device. However, some devices have many components, and some of those components have components, that must be tracked and reported on separately. This sub-team will design a structure to support these requirements.
- CDRH Pilot
  - Since a CDISC-conformant full submission has never been sent before to CDRH, the next logical step would be to do a pilot of CDISC medical device data with CDRH. Again, CDRH does receive SDTM-based domains, but a planned, fully CDISC-conforming submission, including eCTD has never been done before. To that end, at the CDISC Interchange on October 25, 2012, a representative of CDRH mentioned in an FDA panel discussion that he would like to see a pilot of a CDISC data to CDRH. Discussions are underway to develop such a pilot. This pilot would be historic in that it would lay the foundation for CDRH and sponsors to be able to do CDISC-conformant submissions of medical device data (including electronic submission of CDISC-conformant data in an eCTD format).

Finally, much work remains to actually define what compromises a medical device submission in an electronic format. It would be a mistake to simply assume that all of the CDISC standards (e.g., Protocol Representation, ODM, CDASH, ADaM, etc.) developed for pharmaceutical submissions will apply to medical devices. Science and

regulation should drive the standards for medical devices as it did when the CDISC standards for pharmaceuticals were originally developed. The world of medical devices is vast and differs from pharmaceuticals in many respects (Smoak 2007). Thus care must be taken to consider the uniqueness of medical device data in developing a standard for electronic submission of data.

CONCLUSION

The benefits of CDISC standards are well known:

- Improve data collection and data quality
- Allow re-usability of programs to present and analyze data
- Facilitate data exchange
- Enable software tools
- Facilitate review of data by regulatory authorities

Currently these benefits are not being realized by medical device companies or by CDRH. Medical device submissions are at a pivotal point in history. The FDA is poised to require CDISC standards for drug, biologics and devices. It is time for medical devices (companies and CDRH) to begin taking steps towards getting into the CDISC world. Much work remains to be done towards this goal. A pilot of submitting CDISC medical device data to CDRH is in the planning stages. Stay tuned for the results of this ground breaking work!

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